

10

⑪ ① No. 967978

④⑤ ISSUED May 20, 1975

⑥② CLASS 260-476.5
C.R. CL.

⑪ ①

CANADIAN PATENT

⑥④

PREPARATION OF A HYPOCHOLESTEROLEMIC

⑦①

Hazen, George G., Westfield, New Jersey, U.S.A.

Granted to Merck & Co., Inc., Rahway, New Jersey, U.S.A.

②①

APPLICATION No. 125,793

②②

FILED Oct. 21, 1971

③①

PRIORITY DATE Oct. 30, 1970 (85,731) U.S.A.

No. OF CLAIMS 10 - No drawing

14170

A B S T R A C T

A method for the preparation of 2-acetamidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl) acetate which comprises treating 2-acetamidoethyl (4-chlorophenyl)-haloacetate with 3-trifluoromethylphenol or with a salt of 3-trifluoromethylphenol. The 2-acetamidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl)-acetate thus obtained is a hypocholesterolemic and hypolipemic agent which effectively reduces the concentration of cholesterol, triglycerides and other lipids in blood serum.

14170

967978

This invention relates to a novel method for the preparation of 2-acetamidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl)acetate.

There is no clear agreement about the actual
5 role of cholesterol and triglycerides in the localization of atherosclerotic plaques but numerous studies support the concept that cholesterol and triglycerides play a major role in the pathogenesis of atherosclerosis because along with other lipids and fibrin they accumulate in the arterial
10 intima and subintima and produce arterial corrosion.

It is the purpose of this invention to describe a novel method for the preparation of 2-acetamidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl)acetate which product has proved effective in reducing the concentration
15 of cholesterol, triglycerides and other lipids in blood serum. This compound induces a significant reduction in



967978

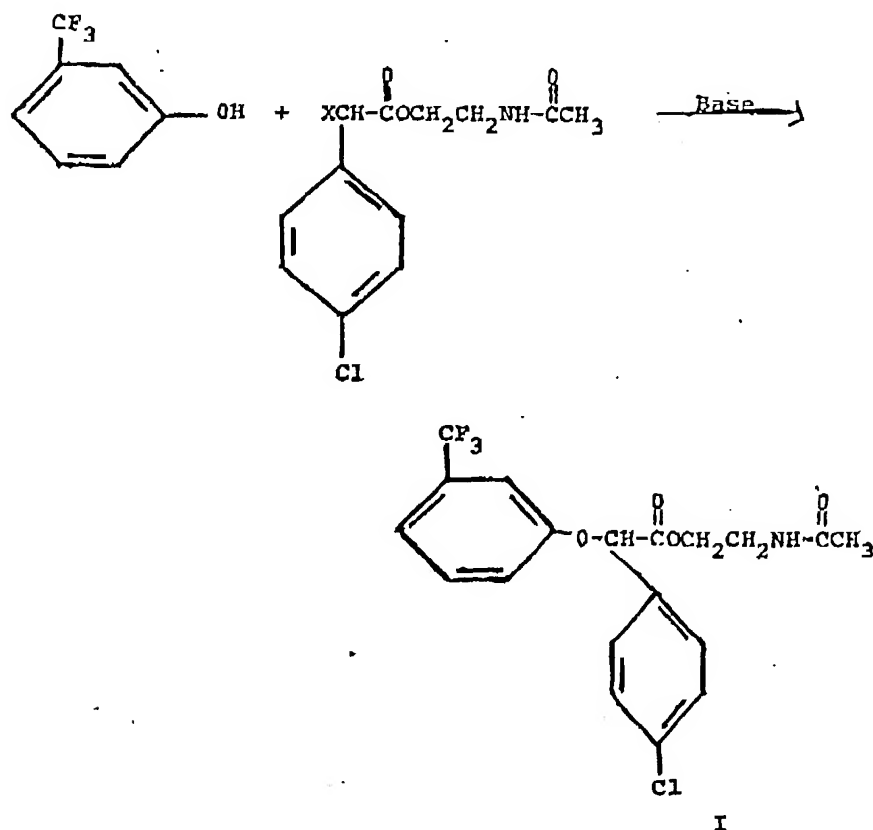
1 cholesterol and triglyceride levels in serum and it
2 achieves this result with little or no irritation to the
3 gastrointestinal tract.

4 According to this invention 2-acetamidoethyl
5 (3-trifluoromethylphenoxy) (4-chlorophenyl)acetate is
6 obtained by treating 2-acetamidoethyl (4-chlorophenyl)-
7 haloacetate with 3-trifluoromethylphenol or with a
8 suitable salt of 3-trifluoromethylphenol. Suitable salts
9 include those obtained by treating 3-trifluoromethylphenol
10 with any organic or inorganic compound having a pH equal
11 to or greater than 7. Typical of these are salts derived
12 from the following basic reagents: the alkali metal or
13 alkaline earth metal hydroxides such as sodium hydroxide,
14 potassium hydroxide, calcium hydroxide, magnesium hy-
15 droxide, and the like, alkaline metal or alkaline earth
16 metal carbonates or bicarbonates such as sodium carbonate,
17 potassium carbonate, calcium carbonate, sodium bicarbonate
18 potassium bicarbonate, and the like, basic metal oxides
19 such as sodium oxide, potassium oxide, calcium oxide,
20 cadmium oxide, gold oxide, silver oxide, and the like,
21 tertiary organic bases, for example, tertiary alkylamines
22 such as trimethylamine, triethylamine, pyridine, and the
23 like, quaternary ammonium bases, for example, tri-lower
24 alkylammonium alkoxides such as trimethylammonium
25 methoxide, triethylammonium ethoxide, and the like or
26 alkali metal or alkaline earth metal alkoxides such as
27 sodium methoxide, sodium ethoxide, potassium ethoxide,
28 potassium tertiary-butoxide and the like. Alternatively,

14170

967978

1 in lieu of a salt of 3-trifluoromethylphenol as the
2 reactant, the said phenol may be employed per se in the
3 process. However, in practice, when 3-trifluoromethyl-
4 phenol is employed it is usually advantageous to con-
5 duct the reaction in the presence of a base. The use
6 of a basic reagent is not critical to the process but,
7 in general, it does serve to promote the reaction and
8 increase the product yield. The following equation
9 illustrates this method of preparation, i.e., using
10 3-trifluoromethylphenol in the presence of base, however,
11 it is to be understood that any salt of 3-trifluoro-
12 methylphenol, such as those defined above, or simply
13 3-trifluoromethylphenol per se may also be employed in
14 otherwise similar process to afford an identical product
15 (I):



967978

14170

1 wherein X is halo, for example, chloro, bromo, fluoro or
2 iodo, and the like and the basic reagent (i.e., "Base")
3 is any organic or inorganic compound having a pH equal
4 to or greater than 7. Thus, suitable bases include, for
5 example, any alkali metal or alkaline earth metal alkoxide,
6 carbonate, bicarbonate or hydroxide such as sodium
7 methoxide, potassium methoxide, calcium ethoxide, sodium
8 ethoxide, sodium carbonate, potassium carbonate, calcium
9 carbonate, sodium bicarbonate, potassium bicarbonate,
10 sodium hydroxide, potassium hydroxide or calcium
11 hydroxide, any suitable tertiary amine, for example, a
12 trialkylamine such as trimethylamine, triethylamine and
13 the like, an heterocyclic amine such as pyridine or
14 quinoline and the like, basic metal oxides such as
15 sodium oxide, potassium oxide, calcium oxide, cadmium
16 oxide, gold oxide, silver oxide and the like or quaternary
17 ammonium bases, for example, tri-lower alkylammonium
18 alkoxides such as trimethylammonium methoxide, triethyl-
19 ammonium ethoxide and the like.

20 The choice of a solvent is not critical to the
21 reaction and, in general, the process may be conducted
22 in any suitably inert medium in which the reactants are
24 reasonably soluble. Suitable solvents include for
25 example, tetrahydrofuran, methylene chloride or hydro-
26 carbons of the aliphatic, acyclic and aromatic variety
27 which are pentane, hexane, decane, dodecane, cyclohexane,
28 benzene, toluene, xylene and the like or alkanols, for

967978

14170

1 example, lower alkanols such as methanol, ethanol and
2 the like. However, the synthesis does proceed most
3 advantageously in hydrocarbons of the type described
4 above and, therefore, the use of such media constitutes
5 a preferred embodiment of this invention. Also the
6 process may be conducted at ambient temperatures but,
7 in practice, the reaction is facilitated by the applica-
8 tion of heat. In general, it is most desirable to employ
9 temperatures in the range of from about 40°C. up to
10 the reflux temperature of the reaction mixture over an
11 extended period of from about one to twenty hours.

12 The 2-acetamidoethyl (3-trifluoromethylphenoxy)
13 (4-chlorophenyl)acetate product of this invention is a
14 crystalline solid which may be purified by recrystalliza-
15 tion from a suitable solvent or from a mixture of solvents
16 as, for example, by recrystallization from a lower alkanol
17 such as methanol, ethanol or isopropanol and the like or
18 from a mixture of said alkanols.

19 The 2-acetamidoethyl (4-chlorophenyl)halo-
20 acetate, halide employed as the starting material in the
21 process of this invention is obtained by treating 4-chloro-
22 phenylacetic acid (II, infra) with an halogenating agent
23 to afford the corresponding 4-chlorophenylacetyl halide
24 intermediate, which intermediate is then treated with
25 a second halogenating agent capable of substituting halogen
26 for hydrogen on the alpha carbon of the acid halide
27 nucleus. The (4-chlorophenyl)haloacetyl halide thus
28 obtained is then treated with 2-acetamidoethanol in the

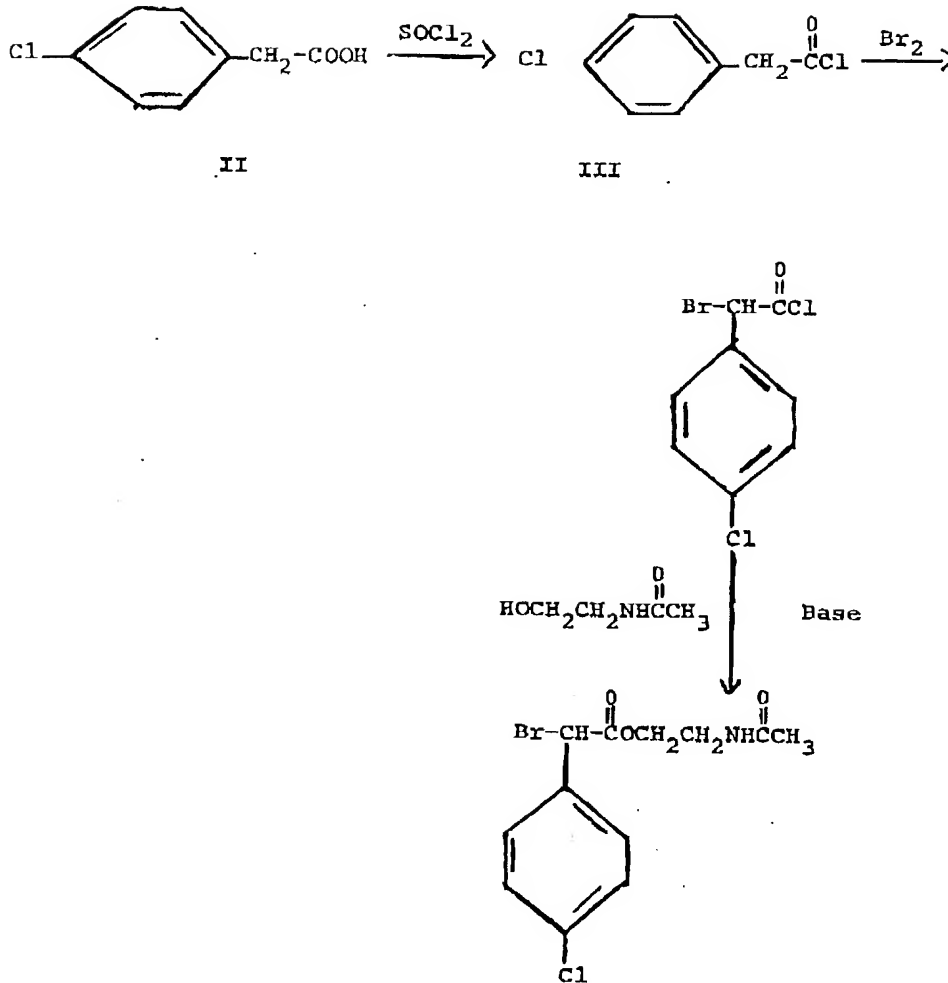
967978

14170

1 presence of a base such as pyridine or sodium carbonate
2 to yield the desired 2-acetamidoethyl (4-chlorophenyl)-
3 haloacetate. In this synthesis the initial halogenation
4 step, which results in the conversion of 4-chlorophenyl-
5 acetic acid (II) to its acid halide, may be carried out
6 with any reagent capable of converting carboxylic acids
7 to their corresponding acid halides. Suitable reagents
8 thus include, for example, the thionyl halides such as
9 thionyl chloride, thionyl bromide and the like. The
10 4-chlorophenylacetyl halide thus obtained may then be
11 isolated and purified or, as generally occurs in practice,
12 the said 4-chlorophenylacetyl halide intermediate is
13 allowed to remain in solution and the reaction mixture
14 is treated with a second halogenating agent capable of
15 converting the said acid halide to the desired (4-chloro-
16 phenyl) haloacetyl halide intermediate. Suitable halogenat-
17 ing agents which may be used in this step include, for
18 example, bromine and chlorine and the like. The following
19 equation, wherein the halogenating agents employed are
20 thionyl chloride and gaseous bromine, respectively,
21 illustrate this method of preparation; however, it is
22 to be understood that any other functionally equivalent
23 reagents may be substituted therefor in an otherwise
24 similar process to afford an identical compound:

967978

14170



1 The following examples illustrate the process
 2 of this invention. However, the examples are illustrative
 3 only and this invention should not be construed as being
 4 limited thereto since other reaction conditions and other
 5 functionally equivalent reagents may be substituted there-
 6 for to afford an identical 2-acetamidoethyl (3-trifluoro-
 7 methylphenoxy) (4-chlorophenyl)acetate product.

14170

967978

1 EXAMPLE 12 2-Acetamidoethyl (3-Trifluoromethylphenoxy) (4-Chloro-
3 phenyl)acetate4 Step A: (4-Chlorophenyl)bromoacetyl Chloride

5 4-Chlorophenylacetic acid (170 g., 1.0 mole)
6 and thionyl chloride (150 g., 1.25 mole) are placed in
7 a 2-liter flask fitted with a stirrer, reflux condenser
8 and dropping funnel. The mixture is stirred and heated
9 at reflux for two hours with stirring while bromine
10 (160 g., 1.0 mole) is added from the dropping funnel
11 over a three-hour period. Heating under reflux is
12 continued for 20 hours. The volatiles are then removed
13 at the aspirator and dry benzene (500 ml.) is added and
14 evaporated in vacuo. The 2.68 g. of (4-chlorophenyl)-
15 bromoacetyl chloride thus obtained is in the form of a
16 brown oil.

17 Step B: 2-Acetamidoethyl (4-Chlorophenyl)-
18 bromoacetate

19 A solution of (4-chlorophenyl)bromoacetyl
20 chloride (268 g., 1.0 mole) in 415 ml. of ether is added
21 to a mixture of 2-acetamidoethanol (103 g., 1.0 mole),
22 dimethylformamide (1164 ml.) and pyridine (90 ml.) at 5°C.
23 over a 30-minute period. The reaction mixture is stirred
24 and protected from atmospheric moisture during the
25 addition. After stirring an additional hour at 5°C.,
26 the reaction mixture is warmed to room temperature and
27 allowed to stand for 16 hours. Water (2 liters) and
28 ether (1.66 liters) are added and the resulting aqueous

14170

967978

1 layer is separated and extracted twice with 1.66 liters
2 of ether. The ether extracts are then combined and
3 dried over sodium sulfate. The ethereal solution is
4 concentrated, flushed with ether and the concentrate is
5 diluted with 200 ml. of methanol. The methanolic
6 solution of 2-acetamidoethyl (4-chlorophenyl)bromo-
7 acetate thus obtained is used directly in the next step.

8 Step C: 2-Acetamidoethyl (3-Trifluoromethyl-
9 phenoxy) (4-Chlorophenyl)acetate

10 3-Trifluoromethylphenol (163.2 g., 1.0 mole)
11 in 200 ml. of benzene is added to a mixture of 1.0 mole
12 of sodium methoxide in 1 liter of benzene. To this
13 mixture is added a solution of 2-acetamidoethyl (4-
14 chlorophenyl)bromoacetate (334.5 g., 1.0 mole) in 200 ml.
15 of benzene. The reaction is heated under reflux for
16 15 hours and then concentrated in vacuo. Ether (4.0
17 liters) and water (1.2 liters) are added to the residue
18 and the organic layer is separated, washed with dilute
19 sodium hydroxide and water and then dried over sodium
20 sulfate. The benzene solution is concentrated to
21 yield 382 g. of crystalline residue, m.p. 82-89°C. Re-
22 crystallization from isopropanol yields 254 g. of 2-acet-
23 amidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl)-
24 acetate, m.p. 93.5-95.5°C.

25 Upon substitution an equimolar amount of the
26 sodium salt of 3-trifluoromethylphenol and benzene (200 ml.)
27 for the 3-trifluoromethylphenol reactant and method of
28 Example 1, Step C and following the procedure described

14170

967978

therein there is thus obtained 2-acetamidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl)acetate. Recrystallization from ethanol affords substantially pure 2-acetamidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl)acetate, m.p. 92-94°C.

EXAMPLE 2

2-Acetamidoethyl (3-Trifluoromethylphenoxy) (4-Chlorophenyl)-acetate

Step A: 4-Chlorophenylacetyl Chloride and (4-Chlorophenyl)bromoacetyl Chloride

10 Thionyl chloride (13.0 g., 0.117 mole) was added to 4-chlorophenylacetic acid (17.06 g., 0.1 mole) and the resulting mixture was stirred and brought to boiling. The mixture was then boiled under reflux for one-half hour and cooled to afford a solution of 4-chlorophenylacetyl chloride.

Bromine (20.0 g., 0.125 mole) was added to the cooled solution of 4-chlorophenylacetyl chloride and the resulting mixture was protected from moisture and heated at 105°C. under reflux for three hours. The resulting mixture was then subjected briefly to vacuum distillation to remove low boiling
20 fractions and three 10 cc. portions of benzene were added and the mixture was distilled at atmospheric pressure to afford (4-chlorophenyl)bromoacetyl chloride.

Step B: 2-Acetamidoethyl (4-Chlorophenyl)-bromoacetate

The crude (4-chlorophenyl)bromoacetyl chloride obtained in Step A was dissolved in benzene (100 cc.) and to this mixture was added 11.0 g. of dried anhydrous

14170

967978

1 sodium carbonate. Ten portions of 2-acetamidoethanol
2 (10.3 g., 0.1 mole) was then added with stirring and
3 cooling to moderate the resulting mildly exothermic re-
4 action. Within 15 minutes after the addition of the
5 last portion of 2-acetamidoethanol the esterification
6 was complete. The 2-acetamidoethyl (4-chlorophenyl)-
7 bromoacetate thus obtained was used directly in the
8 next step.

9 Step C: 2-Acetamidoethyl (3-Trifluoromethyl-
10 phenoxy) (4-Chlorophenyl)acetate

11 The solution of 2-acetamidoethyl (4-chlorophenyl)-
12 bromoacetate from Step B was transferred to a separatory
13 funnel and washed with two 100 cc. portions of water.
14 The flask was then rinsed into the separatory funnel
15 with a mixture of water (10 cc.) and benzene (10 cc.)
16 and left wet. To this solution was added, with stirring,
17 sodium carbonate (11.0 g.) followed by the addition of
18 3-trifluoromethylphenol (16.2 g.). The resulting mixture
19 was heated at reflux for twenty hours and then cooled
20 and extracted with water (100 cc.), ice cold 0.5 N sodium
21 hydroxide (100 cc.), 3% sodium bicarbonate (100 cc.)
22 and 1% sodium chloride (100 cc.). The mixture was then
23 stirred briefly with sodium sulfate (10.0 g.), activated
24 decolorizing charcoal (1.0 g.) was added and the result-
25 ing mixture was filtered and subjected to vacuum dis-
26 tillation to remove benzene. The mixture was then flush-
27 ed with two 50 cc. portions of methyleyclohexane to
28 afford 78% crude 2-acetamidoethyl (3-trifluoromethylphenoxy)

14170

967978

- 1 (4-chlorophenyl)acetate (32.4 g., 0.078 mole) which
2 partially crystallized on standing. Crystallization
3 of the crude product from isopropanol (36 cc.) yielded
4 a 79% recrystallization recovery of 2-acetamidoethyl
5 (3-trifluoromethylphenoxy) (4-chlorophenyl)acetate
6 (25.6 g., 0.0617 mole), m.p. 92-94°C.
7 Any departure from the above description
8 which conforms to the present invention is intended
9 to be included within the scope of the claims.

14170

967978

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method for the preparation of 2-acetamidoethyl-(3-trifluoromethylphenoxy)(4-chlorophenyl)acetate which comprises treating 2-acetamidoethyl(4-chlorophenyl)haloacetate with 3-trifluoromethylphenol in the presence of a base or with a salt of 3-trifluoromethylphenol.

2. The method according to Claim 1 wherein 2-acetamidoethyl(4-chlorophenyl)bromoacetate is treated with 3-trifluoromethylphenol in the presence of a base.

3. The method according to Claim 2 wherein the base is derived from an alkali metal or alkaline earth metal.

4. The method according to Claim 3 wherein the base is an alkali metal alkoxide, alkali metal carbonate, alkali metal hydroxide or alkali metal bicarbonate.

5. The method according to Claim 1 wherein 2-acetamidoethyl(4-chlorophenyl)haloacetate is treated with 3-trifluoromethylphenol in a hydrocarbon solvent and in the presence of a base selected from alkali metal alkoxide or alkali metal carbonate, at a temperature of from about 40°C. up to the reflux temperature of the reaction mixture.

6. The method according to Claim 5 wherein the base is sodium carbonate.

7. The method according to Claim 5 wherein the hydrocarbon solvent is benzene.

8. The method according to Claim 5 wherein the temperature employed is the reflux temperature of the reaction mixture.

14170

967978

9. The method according to Claim 1 wherein 2-acetamidoethyl(4-chlorophenyl)bromoacetate is treated with a salt of 3-trifluoromethylphenol.

10. The method according to Claim 9 wherein the salt of 3-trifluoromethylphenol is an alkali metal or alkaline earth metal salt.



SUBSTITUTE
REMPLACEMENT

SECTION is not Present
Cette Section est Absente